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Human origins

The molecular perspective

Mark Stoneking

The British Prime Minister Sir Winston Churchill (1874–1965) was quoted as saying "the farther backward you can look, the farther forward you are likely to see," which nicely summarizes the usual argument for studying human history. However, even Sir Winston was probably not thinking in terms of the millions of years backward that we have to look to understand the origins of our species. Still, when considering the future of our species, there is merit in examining our beginnings and how we came to be the way we are—such an investigation will not only provide for more informed speculation about our future evolution, but will also highlight important lessons from the history of ideas about our origins.

It is only relatively recently—and only with the advent of molecular genetics—that scientists have largely been able to answer two important questions about human evolution: who are our closest relatives, and what were the circumstances that led to modern humans? Here, I describe how molecular approaches answered these questions and explain why the answers proved to be so difficult.

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I contend that when it comes to considering our own origins we are, consciously or subconsciously, burdened with the idea that we are special creatures, and we expect to see evidence of this in our evolutionary history. In particular, because we like to emphasize our uniqueness, we tend to favour ideas about our origins that emphasize how separate we have become from 'others'—be they other species or even other populations of humans. I do not deny that humans are, at least in some respects, special: we are, after all, the only species that I know of to give lectures or writes essays about its origins. However, the implicit or explicit expectation that our evolutionary history necessitates long periods of separation from others, in order for us to become the special creatures that we know we are, has impeded progress in understanding our origins.

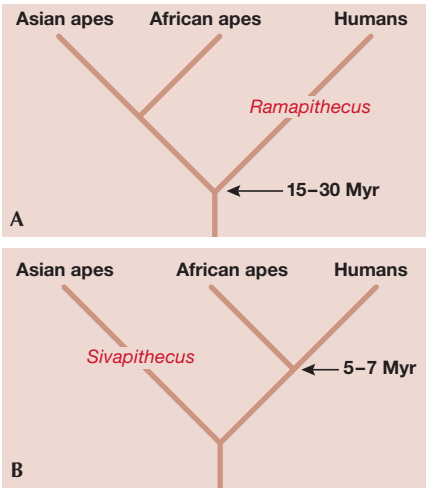

Fig 1 | Two views of our relationships with apes. (**A**) The pre-molecular view, which states that the human lineage diverged initially from the other apes approximately 15–30 million years ago, and that *Ramapithecus* was our ancestor. (**B**) The molecular view, which states that the Asian apes were the first to diverge, followed by human divergence from African apes only approximately 5–7 million years ago. Subsequent fossil findings subsumed *Ramapithecus* into the previously defined taxon *Sivapithecus*, which is thought to be an ancestor of orang-utans. Myr, million years.

This impediment is most apparent in the first question that I address here: who are our closest relatives? The answer that dominated Western Judeo-Christian thinking for centuries and still lingers to this day, is that we are not related to any living creatures; instead, we are special because we alone were created in the image of the Creator—and it is hard to get more special than that. However, the work of the Swedish botanist Carl Linnaeus (1707–1778) and others showed that there was a structure underlying the organization of living beings, which, in turn, led Charles Darwin (1809–1882), Alfred Russell Wallace (1823–1913), Thomas Henry Huxley (1825–1895) and others to realize that this structure was best explained by the process of evolution.

According to these early evolutionists, we are one of three groups of apes: Asian apes (orang-utans and gibbons), African apes (gorillas and chimpanzees) and human apes (Fig 1A). However, we are not particularly closely related to the other apes; our lineage was the first to diverge, and so the Asian apes are more closely related to the African apes and vice versa. According to this view, our lineage diverged from the other apes at least 15 million years ago, and perhaps as much as 30 million years ago. The fossil evidence that supported this view was the remains of a creature called *Ramapithecus*, which was reconstructed to be an upright, walking ancestor of ours that lived approximately 13 million years ago. Therefore, although we are not created in the lofty image of the Creator, we might still take some comfort in the fact that, according

to this view, we are not particularly closely related to other apes; we have had some 15–30 million years to become the special creatures that we know we are.

…"the biochemist knows his molecules have ancestors, while the palaeontologist can only hope that his fossils left descendants"…

This view of our origins held sway in anthropology from around the time of Darwin until the first molecular evidence from Morris Goodman's laboratory in 1963 (Goodman, 1963). Goodman used immunological methods to compare the proteins of Asian apes, African apes and humans, and came to the startling conclusion that it is humans and not Asian apes that are the closest relatives of African apes. However, his methods were qualitative, and did not allow him to quantify the relationship between humans and African apes. That was left to Vincent Sarich and Allan Wilson who used a quantitative immunological method to compare the proteins of Asian apes, African apes and humans in 1967. Similarly to Goodman, they concluded that African apes are more closely related to humans than to Asian apes; moreover, they calculated that the difference between our proteins and those of African apes represents an astonishingly short evolutionary time span: our lineage diverged from the African apes just 5 million years ago, not 15–30 million years ago (Sarich & Wilson, 1967).

The idealized view of science and scientists holds that when data contradict theory, no matter how long or how well that theory has performed, scientists must reject the old theory and come up with a new explanation to account for the new data. The reality, as any scientist knows, is that it is difficult to overcome ideas that have dominated a field for a long time; instead, there is a tendency to reject the data—and the scientists—which do not fit the theory.

The findings of Sarich and Wilson were no exception—their results were dismissed as being too ludicrous to be taken seriously. As one scientist wrote, "[u]nfortunately, there is a growing tendency, which I would like to suppress if possible, to view the molecular approach to primate evolutionary studies as a kind of instant phylogeny. No hard work, no tough intellectual arguments. No fuss, no muss, no dishpan hands. Just throw some proteins into the laboratory apparatus, shake them up, and bingo! We have the answer to questions that have puzzled us for at least three generations" (Buettner-Janusch, 1969). Not one to back down from a fight, Sarich responded in kind with "[o]ne no longer has the option of considering a fossil specimen older than ~8 million years a hominid no matter what it looks like" (Sarich, 1971), and—my favourite—"the biochemist knows his molecules have ancestors, while the palaeontologist can only hope that his fossils left descendants" (Sarich, 1973).

This concept of a single woman as the maternal ancestor of everyone alive today has caused much confusion, not only among the public but also among some biologists who ought to know better

Ultimately, the controversy was resolved not through rhetoric but, of course, through additional data and analyses. The resulting view of our relationship to other apes, which is widely accepted today, is shown in Fig 1B, and is remarkably similar to the results that Sarich and Wilson published more than 40 years ago: namely, that we share a close relationship with African apes, having diverged from them only approximately 5–7 million years ago. So, how does *Ramapithecus*, which was reconstructed to be a bipedal ancestor of ours and dated to about 13 million years ago, fit into this picture? Reconciliation came by way of additional fossil findings that led to a revision of the taxonomy: fossils ascribed to *Ramapithecus* were actually the female members of a previously described genus, *Sivapithecus*, which was reconstructed to be an ancestor of orang-utans. Hence, *Ramapithecus* is no more, and both the revised fossil record and the molecular evidence now support the phylogeny shown in Fig 1B.

Yet this phylogeny raises another question: there are two extant lineages of African apes, gorillas and chimpanzees (including both the common chimpanzee and the bonobo), so which diverged first: humans, gorillas or chimpanzees? At first glance, this would appear to be the type of question that only a scientist would ask because the answer seems obvious: of course humans diverged first, and gorillas and chimpanzees are more closely related—just look at a gorilla, a chimpanzee and then one of us. Yet, again the molecular evidence goes against the conventional wisdom: it turns out that the gorilla lineage diverged first, approximately 7 million years ago, and then our lineage diverged from chimpanzees about 5 million years ago. In the words of the American evolutionary biologist Jared Diamond, we are basically a third type of chimpanzee. I would argue that the realization that we share an astonishingly close common ancestry with African apes, in particular with chimpanzees, is perhaps the most important contribution of molecular biology to the question of our origins, because without this evidence, we would probably still adhere to the view of an old split between us and the other apes as shown in Fig 1A.

The second question that I consider here, from the molecular genetic perspective, is what were the circumstances that led to our species—modern humans? This question is deceptive. The way that it is usually phrased, as above, makes it sound as if we are interested in the origins of a single entity—modern humans—whereas in reality we see an enormous diversity in the physical appearance of humans. So, what we usually want to know is: how did all of this diversity arise? Is it ancient or recent? Does it have a single origin or multiple origins?

There have been many ideas about the origins of modern humans, but they basically all fall into the four main categories depicted in Fig 2. One of the earliest is the candelabra model, which prevailed for decades. According to this model, the common ancestor of human populations from the main regions of the Old World—Africa, Europe, Asia and Australasia—dates back to the late Miocene, perhaps as much as 2 million years ago. As modern humans did not exist at that time, the transformation from our ancestors to modern humans would have occurred independently in four separate regions of the world, at more or less the same time. The candelabra model was most prominently associated with the anthropologist Carleton Coon (1904–1981), and fell out of favour when he used it to promote racist views. According to Coon, the transformation to modern humans occurred first in Europeans, and hence they have had the

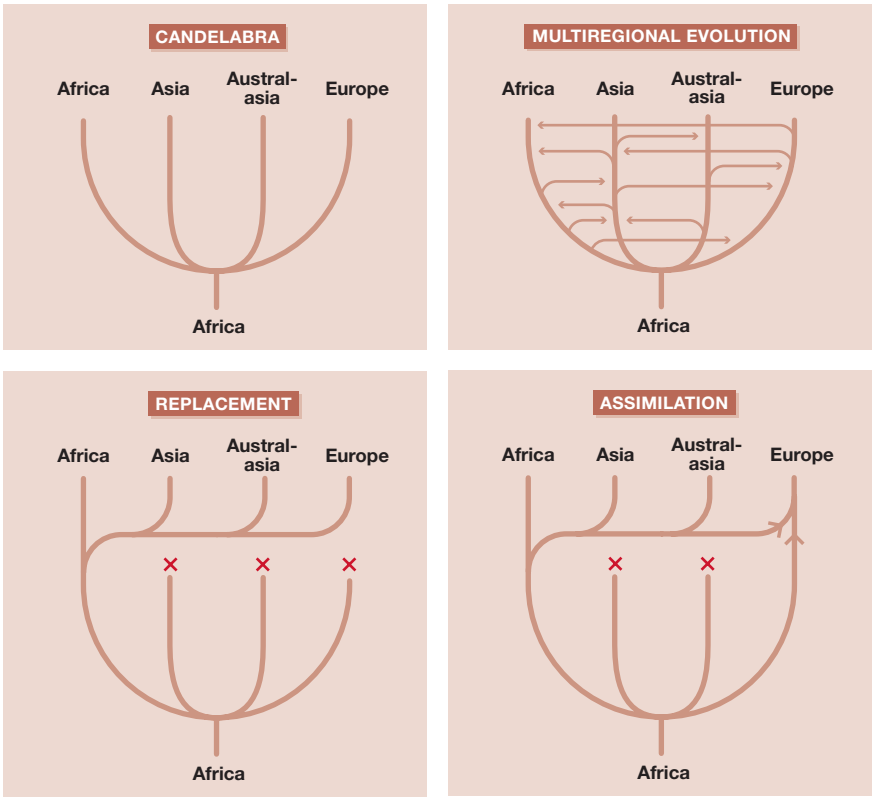

Fig 2 | Four models of the origin of our species. The horizontal arrows in the multiregional evolution model emphasize the role of migration. The absences of similar arrows in the replacement and assimilation models, before the migration out of Africa, are only for clarity, and should not be inferred as indicating absences of migration during this time period.

most time to evolve from their 'primitive' ancestry, whereas Africans were the last to transform into modern humans and therefore have had the least amount of time to shed their primitive ancestry—and in case you were wondering, Carleton Coon was of European ancestry. One can see the same logic at work here as with the early incorrect views about our relationships with apes: namely, the desire to see 'us' as special—where 'us' now refers to Europeans—compared with other groups, because it took a long time for us to become so special.

Regardless of the racist implications of the candelabra model, to my knowledge, no scientist today regards it as a credible explanation of human origins for the simple reason that the biological and genetic changes involved in the transformation to modern humans were too complex to have arisen completely independently in four separate regions of the world. The debate about human origins has therefore revolved around the other three models shown in Fig 2, or variants thereof, which are based on different interpretations of the same fossil evidence.

These indicate that all human evolution took place in Africa until approximately 1.5–2 million years ago, and that between 1.5 million and 50,000 years ago, various waves of migration spread our ancestors, or their relatives, from Africa across the world. There are, however, many different names for various fossil species and just as many arguments for which of these deserve to be called our ancestors. To keep things simple, I will use the term 'archaic human' to refer to anything before the appearance of modern humans that might or might not be our ancestor.

The extent to which earlier migrations contributed to modern humans is the main source of contention among these models. Multiregional evolution, at first glance, appears similar to the candelabra model, in that the main lines of descent within each geographic region are from within that geographic region: modern Africans descend mostly from ancient Africans, modern Europeans descend mostly from ancient Europeans and so on. The main argument for multiregional evolution is the contention that the fossil record shows regional continuity over time. However, an important difference between multiregional evolution and the candelabra model is that the former includes migration between regions as shown by the horizontal arrows in Fig 2, so any important genetic change would have spread quickly. According to multiregional evolution, our ancestors encompass the entire Old World population of archaic humans, which evolved during the past 1.5–2 million years through a complex interchange of species-wide selection for genetic changes that were favourable across all geographic regions, with local selection and/or genetic drift influencing traits specific to particular geographic regions, and migration to avoid the problem of independent evolution of modern humans in different regions of the Old World.

By contrast, the replacement model (Fig 2) argues that the transformation to modern humans occurred in a single population in Africa roughly 200,000–300,000 years ago, which then spread across and out of Africa between 50,000 and 100,000 years ago and replaced completely, without any interbreeding, the archaic populations from earlier migrations from Africa. The evidence in favour of this hypothesis is the fact that the earliest fossils of anatomically modern humans come from Africa, and that early modern human fossils from regions outside Africa tend to be more similar to those from Africa than to archaic human fossils from the same region.

The replacement model is the most extreme version of the out-of-Africa models; others acknowledge that the transformation to modern humans occurred in Africa, but hold that the spread of modern humans was not a complete replacement event, but rather was accompanied by some amount of interbreeding with non-African, archaic humans. I refer to these as assimilation models (Fig 2), which are numerous and differ in where and how much admixture is postulated to have occurred. The fossil evidence cited in favour of a particular assimilation hypothesis is a combination of the evidence for an African origin of modern humans along

with particular traits that are found in both the modern and archaic inhabitants of a particular non-African region.

It must be emphasized that all of these models were initially based on fossil evidence, not molecular evidence. However, I argue that all of these models are really statements about genes; in particular, they can be distinguished by their predictions about the contribution of African genes to the gene pool of non-African populations of modern humans (Fig 3). At one extreme is the candelabra hypothesis, which predicts that there are no African genes outside Africa: modern Europeans got all of their genes from archaic Europeans, modern Asians from archaic Asians and so on. At the other extreme is the replacement model, which predicts that all of us got all of our genes from our African ancestors. In between these two extremes is multiregional evolution, which predicts that archaic Asians, Europeans and Australasians contributed genes to modern humans. Also between the two, but closer to the replacement side, are the assimilation models, which predict that archaic non-Africans contributed some small percentage of our genome.

Fig 3 | The four models of our origins, as distinguished by a schematic indication of the predicted contribution of African genes to non-African populations.

It might well be that some small fraction of our 3 billion nucleotides of DNA comes from Neanderthals and/or some other archaic, non-African population

Therefore, the way to distinguish between these models is to look at our genes, and the first set to be examined in sufficient detail to address this question was the human mitochondrial DNA (mtDNA) genome. This small, compact and circular molecule has several useful properties: it has a high copy number and is located in the cytoplasm with several hundreds to thousands of mtDNA genomes per cell, which makes it relatively easy to isolate and analyse; it has a rapid rate of evolution resulting in many mutations that can be analysed for their distribution within and between populations; and it is maternally inherited without recombination, which means that the only sources of variation between individuals are mutations that arose since they last shared a common maternal ancestor. This latter property has the further virtue that a phylogenetic tree based on mtDNA can be interpreted as the maternal genealogy of our species, and that all of the mtDNA types in the entire population of humans today must trace back to a single common female ancestor—the so-called 'mitochondrial Eve'.

This concept of a single woman as the maternal ancestor of everyone alive today has caused much confusion, not only among the public but also among some biologists who ought to know better. Yet the concept is relatively straightforward: given that there was a single origin of life on this planet that all living things today are derived from, then it has to be the case that all of the variation in any DNA sequence, not just mtDNA, must trace back to a single ancestor at some point in the past. The fact that in the case of mtDNA the ancestor was a woman follows from the maternal inheritance of mtDNA.

However, mitochondrial Eve differs from the biblical Eve in one important aspect: she was not the only woman alive on the planet at the time that she lived; instead, she was a member of a population that included many other women, but they did not contribute mtDNA types to the people living today. If one could follow the descendants of all women who lived at the same time as mitochondrial Eve, generation after generation, sooner or later all of the female descendants of each woman would either have no offspring or only male offspring, resulting in the extinction of that mtDNA lineage.

There are some additional important characteristics of mitochondrial Eve. First, she was probably not the ancestor of any of our other genes—to be sure, all of our genes have common ancestors, but they were undoubtedly different individuals, living at different times and in different places. Second, she was not necessarily the first member of anatomically modern humans, even though one often reads in the popular press that she was the first modern human. There is nothing in the process of random extinction of mtDNA lineages that says that this process had to begin with the first member of our species. For example, some of us carry alleles of genes of the major histocompatibility complex (MHC; which is involved in the immune system) that are more closely related to alleles found in chimpanzees than they are to other human alleles (Gyllensten & Erlich, 1989). This 'trans-species' polymorphism must be older than the species that share the polymorphism, which in this case means more than 5 million years old. Although natural selection has undoubtedly had a role in maintaining such trans-species polymorphisms for millions of years, it is obviously impossible for the ancestor of these genes to have been an anatomically modern human.

Therefore, the fact that all of the variation in our mtDNA types traces back to a single common ancestor is a straightforward consequence of evolutionary theory and is not even particularly interesting. Instead, what is interesting is the question of when and where she lived, and what, if anything, this might tell us about our origins. The first in-depth study of human mtDNA variation, which was carried out by Rebecca Cann and myself when we were graduate students with Wilson in 1987, strongly implied that Africa was the source of all extant human mtDNA diversity, and that this diversity began to arise approximately 200,000 years ago, indicating a recent African origin for mitochondrial Eve (Cann *et al*, 1987).

As with the previous work of Wilson, which showed a close relationship between humans and African apes, the idea of a recent African origin for mitochondrial Eve was again dismissed by some as being too ridiculous to merit any serious consideration. However, there was also legitimate criticism, and the ensuing 20 years have witnessed much debate over such issues as how best to sample human populations to study genetic diversity, the

accuracy of phylogenetic methods for inferring the geographic origin of a DNA ancestor and whether there is a molecular clock—a constant rate of evolution—for human mtDNA and, if so, how fast it 'ticks'. The past 20 years have also witnessed extraordinary advances in molecular genetics, such that it is now routine to sequence the entire mtDNA genome from human population samples, as well as tremendous improvements in the methods used to make inferences about population history from DNA sequence data.

With all of these advances, what do we think now about mitochondrial Eve? All analyses of mtDNA variation in contemporary human populations basically agree: she lived in Africa roughly 150,000–200,000 years ago, and modern humans then began spreading across and out of Africa between 50,000 and 100,000 years ago, with no evidence that any archaic, non-African populations contributed their mtDNA to us—a view that is remarkably similar to that which we published more than 20 years ago.

> **"There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact"**

The inference of a recent African origin for mitochondrial Eve received additional support in 1997 with the first retrieval of an authentic mtDNA sequence from a Neanderthal fossil. This sequence fell outside the range of variation observed in modern human mtDNA, exactly as predicted by the recent African origin hypothesis. Sequences of mtDNA have now been obtained from around a dozen different Neanderthals, and they all group together and are distinct from our own mtDNA sequences (Krause *et al*, 2007).

Even if the case for a recent African origin of mitochondrial Eve is incontrovertible, does this mean that the replacement model is correct? Not necessarily—there is more to us than just mtDNA. Therefore, we need to study other parts of our genome, and the next one to be looked at in great detail was the Y chromosome. This is the male counterpart to mtDNA because it is found only in males and is passed down from fathers to sons, meaning that the Y chromosome—or Y-DNA, for short—can be used to trace our paternal history. Studies of human Y-DNA at first lagged behind mtDNA because of difficulties in detecting any variation. Around 2001, new molecular genetic techniques led to the discovery of a wealth of variation on the Y chromosome and opened up detailed studies of Y-DNA variation. These studies found that the common ancestor of the Y chromosomes that modern humans carry today most likely lived in Africa about 60,000–100,000 years ago (Underhill *et al*, 2001). This more recent date for 'Y-DNA Adam' than for mitochondrial Eve might reflect a different demographic history. In particular, this more recent date could reflect the sad truth that in most human societies, fewer males than females get to have offspring. Yet, regardless of the explanation, there is a strong concordance in the results, which support a recent African origin for both mitochondrial Eve and Y-DNA Adam.

There have also been numerous studies of other genes, most of which support a recent African origin and, hence, the replacement model; however, a few do not. These studies generally claim that because a particular mutation is found only outside Africa, and is older than modern humans, it must have arisen in an archaic population outside Africa and been transmitted to modern humans coming from Africa, thereby supporting assimilation models. Some reports of old, non-African mutations have fallen by the wayside as subsequent work has found them in Africa, or because they are not so old after all and could have arisen in modern humans coming from Africa, or because selection is influencing the variation of the genes in question. Moreover, it has recently been shown that random events have such a large role in influencing the patterns of variation from gene to gene that even under the replacement model, some mutations are expected, by chance, to have the pattern described above: namely, being old but not found in African populations today (Fagundes *et al*, 2007).

In conclusion, the genetic data do not currently allow us to distinguish between the replacement model and assimilation models. It might well be that some small fraction of our 3 billion nucleotides of DNA comes from Neanderthals and/or some other archaic, non-African population. However, further analyses of DNA variation in contemporary human populations, as well as exciting new developments in ancient DNA analyses—such as the Neanderthal Genome Project—should provide an answer to this question.

So, what does the future hold for us? I am not so bold as to make predictions about our future evolution. As Mark Twain wrote on the pitfalls of extrapolating from current trends: "There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact." Yet one prediction that is safe to make is that the enduring legacy of using molecular genetic analyses to understand our evolutionary past —and perhaps even our future—will continue.

ACKNOWLEDGMENTS

I thank B. Pakendorf for reading and commenting on this paper, and S. Michaelis and R. Carl for producing Fig 2.

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doi:10.1038/embor.2008.64